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Reconciling the different faces of hippocampal theta: the role of theta oscillations in cognitive, emotional and innate behaviors

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Highlights

- Theta rhythm is crucial for cognitive functions: memory, spatial and time coding
- Theta rhythm is crucial for anxiety-related behaviours
- Theta oscillation properties (phase, frequency, amplitude) are linked with behaviors
- Parallel emergence of hippocampal theta oscillations and behaviors during development

Abstract

The theta oscillation (5-10 Hz) is a prominent behavior-specific brain rhythm. This review summarizes studies showing the multifaceted role of theta rhythm in cognitive functions, including spatial coding, time coding and memory, exploratory locomotion

and anxiety-related behaviors. We describe how activity of hippocampal theta rhythm generators - medial septum, nucleus incertus and entorhinal cortex, links theta with specific behaviors. We review evidence for functions of the theta-rhythmic signaling to subcortical targets, including lateral septum. Further, we describe functional associations of theta oscillation properties - phase, frequency and amplitude - with memory, locomotion and anxiety, and outline how manipulations of these features, using optogenetics or pharmacology, affect associative and innate behaviors. We discuss work linking cognition to the slope of the theta frequency to running speed regression, and emotion-sensitivity (anxiolysis) to its y-intercept. Finally, we describe parallel emergence of theta oscillations, theta-mediated neuronal activity and behaviors during development. This review highlights a complex interplay of neuronal circuits and synchronization features, which enables an adaptive regulation of multiple behaviors by theta-rhythmic signaling.

Keywords: hippocampus, entorhinal cortex, memory, resonance, grid cells, place cells, behaving mice, anxiety, speed, optogenetics

1.1 Behavioral correlates of theta rhythm: Introduction

This review attempts to integrate cognitive, emotional and innate behaviour control-related aspects of hippocampal function, highlighting the crucial role of hippocampal theta rhythm in all of these functions. Research activities on the hippocampus, and hippocampal theta, tend to cluster into related fields. One cluster consists of spatial cognition, intensely studied in rodents, with the work on spatial memory representing a large overlap with a more general memory-oriented field. The field of locomotion and sensorimotor integration overlaps with the spatial cognition field of this first cluster: this is because spatial researchers increasingly recognize that an important contribution to spatial localization emerges from locomotion-derived computations of distance and direction travelled. For the spatial cognition field, then, locomotion-related inputs into the hippocampus are required to update location, and outputs to locomotor regions are required to direct the animal *where* to go. However, the idea that the hippocampus may control locomotion in a more fundamental way has persisted, largely inspired by Vanderwolf (1969) arguing that the key correlate of theta

was voluntary locomotion. In this review, we consider evidence for both the spatial cognition, and the locomotor control, fields of research.

A rather distant research cluster consists of emotion-related fields investigating anxiety, stress and depression. It is worth remembering that the ‘Papez circuit’ approach to limbic anatomy posited the hippocampus as an emotional centre. Broadly speaking, there has been minimal conversation between the cognition-locomotion and emotion-related ‘faces’ of theta. In this review, we not only attempt to highlight interesting work in both clusters, we set out the beginnings of an approach that may begin to bridge these seemingly-separate research areas. We start from the perspective that the hippocampal theta oscillation, while crucially subserving both cognition-locomotion and emotion-related functionality, is an essentially unitary phenomenon. Taking the theta frequency to running speed regression as a starting point, we describe theoretical and empirical work linking a cognition-locomotion component to the slope of this regression, and an emotion-sensitivity component (here, in particular, anxiolysis) to its y-intercept. Our discussion of the development of theta up to adulthood considers both the slope and y-intercept components.

Theta rhythm shows intriguing correlations with a range of different behaviors that include both aspects of movement and of memory function. Extensive data shows theta frequency oscillations in the local field potentials in the hippocampus across species (Green and Arduini, 1954), with similar mechanisms implicated in a range of frequencies labelled as theta (Buzsaki, 2002). Theta rhythm also appears in rat entorhinal cortex (Alonso and Garcia-Austt, 1987; Brandon et al., 2011; Mitchell and Ranck, 1980) and medial prefrontal cortex (Jones and Wilson, 2005; Lee et al., 2005). Intracranial electrodes implanted to detect seizure activity in humans show cortical theta rhythm oscillations associated with performance of memory tasks in humans (Kahana et al., 1999; Lega et al., 2011; Raghavachari et al., 2001; Rizzuto et al., 2006).

Theta rhythm correlates with a range of movement behaviors (Bland and Oddie, 2001; Vanderwolf, 1969; Whishaw and Vanderwolf, 1973) including running on a track (O’Keefe and Nadel, 1978; Skaggs et al., 1996), running wheel (Buzsaki et al., 1983; Hyman et al., 2003), treadmill (Brankack et al., 1993; Fox et al., 1986), and anticipates changes in movement (Morris and Hagan, 1983). Frequency and amplitude of rat theta

increases with running speed (Jeewajee et al., 2008a; Maurer et al., 2005; Rivas et al., 1996; Whishaw and Vanderwolf, 1973), suggesting a role in coding of velocity and location (O'Keefe and Nadel, 1978). We consider theta's links to locomotion, running speed, and location in sections 2 and 4.

Theta rhythm in the hippocampus also correlates with learning and memory function (Berry and Thompson, 1978; Givens and Olton, 1990; Griffin et al., 2004; Seager et al., 2002; Vertes and Kocsis, 1997; Winson, 1978). Lesions of the medial septum and fornix cause memory impairments in tasks including delayed spatial alternation (Aggleton et al., 1995; Givens and Olton, 1990), spatial reversal (M'Harzi et al., 1987), and the 8-arm radial maze (Mitchell et al., 1982). The reduction of theta rhythm correlates with the amount of memory impairment (Givens and Olton, 1994; Winson, 1978). Temporary inactivation of the medial septum causes impairments of spatial memory and also reduces theta rhythm in both the hippocampus (Brioni et al., 1990; Chrobak et al., 1989; Mizumori et al., 1990) and entorhinal cortex (Jeffery et al., 1995). We consider theta's links to learning and memory in section 5.

Less studied than movement and memory correlates, theta rhythm has also been linked to arousal (e.g. Green and Arduini, 1954), and to behavioural inhibition and anxiety (Gray, 1982; Sainsbury, 1998). Benzodiazepines, anxiolytic drugs, reduce both theta frequency and hippocampal-sensitive behavioural inhibition in fixed-interval responding (Woodnorth and McNaughton N, 2002). These links are further explored in sections 3 and 6 below.

2.1 Theta rhythm and the coding of spatial location.

The role of theta rhythm in memory function may be related to a potential role of theta rhythm in the coding of the dimensions of space and time that are essential to episodic memory function (Tulving, 1983). Evidence for this role includes recordings showing a potential role of theta in the coding of a range of spatial dimensions. Numerous studies have explored the phenomenon of place cells in the hippocampus, which respond selectively when a rat visits specific locations in an environment (O'Keefe, 1976; O'Keefe and Dostrovsky, 1971b; Skaggs et al., 1996). Hippocampal place cells show a strong rhythmicity of firing at theta rhythm frequencies, as shown by the autocorrelation of spike times (Climer et al., 2015; O'Keefe and Burgess, 2005;

O'Keefe and Recce, 1993). Place cells also show more fine-grained temporal coding of spike timing relative to the phase of theta rhythm in the form of theta phase precession (O'Keefe and Recce, 1993; Skaggs et al., 1996). When a rat runs through its firing field, a place cell initially spikes at late phases of the theta cycle, and then shifts to progressively earlier phases as the rat continues through the place field (Huxter et al., 2003; O'Keefe and Recce, 1993; Skaggs et al., 1996).

A relationship between spatial coding and theta rhythm also appears in recordings of grid cells in the entorhinal cortex in rats (Hafting et al., 2008; Moser and Moser, 2008). Grid cells respond as a rat visits a regular array of locations in the environment described as falling on the vertices of tightly packed equilateral triangles (Fyhn et al., 2004; Hafting et al., 2008; Hafting et al., 2005). Grid cells also show strong theta rhythm firing, and grid cells in specific layers will show theta phase precession (Hafting et al., 2008). Each time a rat passes through the firing field of a grid cell, the spiking starts at late phases of the LFP theta cycle, and shifts to earlier phases of the theta cycle (Climer et al., 2013; Eggink et al., 2014; Hafting et al., 2008; Jeewajee et al., 2014).

Evidence that the spatial coding of grid cells might depend upon theta rhythm oscillations comes from studies that blocked entorhinal theta rhythm oscillations using infusion of pharmacological agents into the medial septum (Brandon et al., 2011; Koenig et al., 2011). The blockade of theta rhythm oscillations was accompanied by loss of spatial periodicity of grid cells, without loss of head direction cell selectivity by neurons (Brandon et al., 2011). This loss of grid cell spatial coding during the loss of theta rhythm oscillations suggests an important role for theta rhythm in spatial coding, and could explain the spatial memory impairments seen during inactivation of the medial septum (Chrobak et al., 1989). Surprisingly, inactivation of the medial septum does not appear to block the firing of place cells in novel or familiar environments (Brandon et al., 2014).

2.2 Theta rhythm and the coding of running speed.

In addition to the coding of location by place cells and grid cells, extensive experimental data also indicates a relationship between theta frequency and the spatial dimension of running speed. Multiple studies have shown that the frequency and amplitude of theta rhythm in the field potential increases with running speed (Jeewajee

et al., 2008a; Maurer et al., 2005; Rivas et al., 1996; Whishaw and Vanderwolf, 1973), suggesting a role in coding of speed. The difference in field potential frequency is a change of about one hertz over a full range of running speeds from 5 cm/sec to 30 cm/sec, but these effects show robust statistical significance. Interestingly, coherence of theta oscillations (Royer et al., 2010; Sabolek et al., 2009) and the relationship between theta power and locomotion speed (Hinman et al., 2011) decreases along the septo-temporal (aka dorsoventral) axis (Patel et al., 2012). Theta power is significantly lower in the ventral (temporal) hippocampus, where the proportion of theta-rhythmic neurons is lower, compared to the dorsal (septal) hippocampus (Royer et al., 2010).

Neurons in the hippocampal formation and entorhinal cortex also directly code running speed with changes in firing rate (Hinman et al., 2016; Kropff et al., 2015; Lever et al., 2003; O'Keefe et al., 1998; Wills et al., 2012). Neurons that code running speed include grid cells and head direction cells (Hinman et al., 2016; Kropff et al., 2015), whereas neurons sensitive to running speed that do not code other spatial dimensions are referred to as speed cells (Kropff et al., 2015). In addition to these changes in firing rate, many entorhinal neurons also show changes in firing rhythmicity, commonly increasing their frequency with an increase in running speed (Hinman et al., 2016; Jeewajee et al., 2008a; Stensola et al., 2012). This change in rhythmicity with running speed is lost during pharmacological inactivation of the medial septum, even though the change in firing rate is not lost (Hinman et al., 2016). Given that this same inactivation disrupts grid cells, this could imply that speed-rate modulation is dispensable, while theta frequency-speed modulation is critical for normal grid cell function.

The relationship between running speed and theta rhythmicity has been explored in other pharmacological studies of the medial septum. These studies were motivated by studies showing that circuits in the medial septum that regulate theta rhythm are implicated in both memory function (Chrobak et al., 1989), as described above, as well as in the regulation of anxiety (McNaughton N. and Coop, 1991). An intriguing connection between these potential roles concerns impairments in memory encoding and spatial navigation, produced, respectively, by the benzodiazepines (Ghoneim and Mewaldt, 1990) and serotonin 5-HT_{1A} receptor agonist buspirone (McNaughton N. and Morris, 1992), drugs used to treat anxiety.

Systemic injections of anxiolytic drugs cause a consistent reduction in the frequency of theta rhythm oscillations across a range of running speeds (Wells et al., 2013). Because the effect is consistent across running speeds, this results in a shift of the y-intercept of a regression line fitting frequency to running speed, without changing the slope of the regression line. Consistent with this result in the hippocampus, recordings of local field potentials and spiking rhythmicity in the entorhinal cortex show a systematic decrease in theta frequency across a range of running speeds, as presented in conference abstracts (Monaghan et al., 2015; Monaghan et al., 2014). In contrast, the novelty of the environment has been shown to change the slope of the relationship between frequency and running speed (Wells et al., 2013). This effect on slope is consistent with the fact that novelty will increase the spacing and size of grid cell firing fields in entorhinal cortex (Barry et al., 2012b).

A sophisticated computational model has linked many aspects of the experimental data on theta rhythm and the coding of spatial location and running speed, using the phenomenon of oscillatory interference (Burgess, 2008; Burgess et al., 2007). This model arose from the initial model of theta phase precession that predicted multiple spatial firing fields (O'Keefe and Recce, 1993). In this model, velocity shifts the theta frequency of oscillators, such that the relative phase of oscillations codes the spatial position of the animal, and summation of oscillations generates grid cell firing fields. This model directly demonstrates the potential link between coding of space and the phenomenon of theta phase precession (Hafting et al., 2008). The model also effectively predicted a relationship between rat running speed and the spacing of grid cell firing fields (Jeewajee et al., 2008a; Stensola et al., 2012), as well as the difference in slope of theta phase precession at different dorsal to ventral positions in entorhinal cortex (Hafting et al., 2008) and hippocampus (Kjelstrup et al., 2008). Consistent with the model, modulation of spiking frequency by the cosine of head direction has been shown in theta rhythmic neurons of the hippocampus and medial septum (Blair et al., 2008; Welday et al., 2011). This model links the circuit dynamics of theta rhythm to the coding of space for behavior (Blair et al., 2008; Blair et al., 2007; Hasselmo, 2008; Hasselmo and Brandon, 2012; Hasselmo et al., 2007; Welday et al., 2011). The specificity of firing could be enhanced by reset by sensory input about environmental barriers (Bush and Burgess, 2014; Hardcastle et al., 2015).

This model is also supported by some aspects of intracellular physiological data, including the difference in the frequency of resonance and subthreshold membrane potential oscillations for entorhinal neurons at different anatomical positions (Giocomo et al., 2007) that has been extensively replicated (Boehlen et al., 2010; Dodson et al., 2011; Giocomo and Hasselmo, 2008a; Giocomo and Hasselmo, 2008b; Giocomo and Hasselmo, 2009; Heys et al., 2010; Pastoll et al., 2012; Shay et al., 2012). Resonance correlates with the time course of rebound from hyperpolarization, and rebound spiking might contribute to grid cell firing (Ferrante et al., 2016; Shay et al., 2016).

3.1 Subcortical circuits underlying the behavioral correlates of theta rhythm

The subcortical circuits involved in generating and regulating theta oscillations are multiple, complex, and have still not yet been fully delineated. Theta rhythm is controlled by several subcortical nuclei. Medial septum, the supramammillary nucleus, nucleus incertus and posterior hypothalamus are involved in theta generation whereas serotonin-containing neurons of the median raphe nucleus promote non-theta state in the hippocampus (reviewed in Kirk, 1998; Oddie and Bland, 1998; Pan and McNaughton N, 2004; Vertes and Kocsis, 1997; Vinogradova 1995). The medial supramammillary nucleus (SuM) sends projections to the medial septum (Vertes, 1992), SuM cells exhibit theta-rhythmic activity and are phase-locked to hippocampal theta (Kirk and McNaughton N, 1991; Kocsis and Vertes 1997). Median raphe nucleus (MR) promotes hippocampal non-theta (desynchronized) state (Graeff et al., 1980). MR lesions induced hippocampal theta activity during immobility (Maru et al., 1979), suggesting an inhibitory influence of MR on the hippocampal theta generation. MR projects strongly to the medial septum and hippocampus (McKenna and Vertes 2001). Majority of neurons in median raphe nucleus (MR) exhibit theta-associated theta activity (Viana Di Prisco et al., 2002). Pharmacologically induced blockade of the MR elicited theta-bursts in the medial septum and hippocampal theta (Kitchigina et al., 1999; Kinney et al., 1995). Hippocampal theta was also produced by pharmacological suppression of the median raphe nucleus with serotonin_{1A} agonists (Vertes et al., 1994), whereas non-serotonergic (possibly glutamatergic) median raphe projections to the MS can facilitate the generation of hippocampal theta in the absence of medial septal cholinergic tone (Crooks et al., 2012). Key regions regulating theta oscillations are also connected with

other nuclei, including interpeduncular nucleus (IP), which is reciprocally connected with the supramammillary nucleus (Shibata et al., 1986), the nucleus incertus (Ma, Gundlach, 2015) and median raphe (reciprocal inhibitory connections, Lima et al., 2017), suggesting that IP might also be involved in regulation of theta oscillations.

A comprehensive discussion of these circuits is beyond the scope of this review, and consistent with our functional focus on spatial cognition and memory, locomotion, and emotion-sensitivity, we focus upon three subcortical regions: 1) the medial septum and diagonal band of Broca (hereafter ‘medial septum’); 2) the lateral septum; and 3) the nucleus incertus. We review the medial septum (section 3.2), because it is the most important integrator of multiple ascending influences upon theta, and is crucial for hippocampal theta, and thus all theta’s functional associations. We discuss the lateral septum (section 4.2), mainly for its role in the links between theta and locomotion, after first reviewing more generally the links between hippocampal activity, theta and locomotion (section 4.1). The lateral septum’s importance arises in part from its position in receiving massive projections from the hippocampus, and sending projections to the ventral tegmentum area and lateral hypothalamus. We discuss the nucleus incertus (section 3.3), which has dense projections to the medial septum and ventral hippocampus, not just to draw attention to recent work on this hitherto little-studied region, but in particular to highlight its relevance to probing mechanisms underlying links between hippocampal theta on the one hand, and arousal, stress and anxiety on the other.

3.2 Subcortical circuits underlying the behavioral correlates of theta rhythm: medial septum

As noted above, theta oscillations in dorsal hippocampus have long been associated with exploratory activity. The frequency and amplitude of hippocampal theta oscillations is proportional to running speed (McFarland et al., 1975), see section 2.2. Circuits involved in theta rhythm generation receive multiple inputs from brain regions coding sensory- and motor-related information (Bland and Vanderwolf, 1972a; Oddie and Bland, 1998; Vertes et al., 2004), that can underlie adjustment of theta oscillations to behavioral states. The activity of many neurons in theta-generating regions, including hippocampus (Geisler et al., 2010; Huxter et al., 2003; McNaughton B.L. et al., 1983),

medial septum (MS) (Justus et al., 2017) and medial entorhinal cortex (MEC) (Hinman et al., 2016; Kropff et al., 2015), correlates with running speed. Lesions of MS greatly impair hippocampal theta oscillations (Buzsaki et al., 1983; Rawlins et al., 1979). Locomotion-dependent activity of MS cells, interconnected with subcortical regions, including several hypothalamic nuclei, is thought to underlie matching of theta frequency to changing running speed (Bland et al., 2006). Optogenetic stimulation of MS cells at theta frequency (without specificity for cell type) in freely moving rats affected hippocampal theta oscillations in a speed-dependent manner, being stronger at slower speeds (Blumberg et al., 2016).

Several studies have focused on dissecting out the roles of different cell types in MS. The MS comprises several cell types, projecting in other brain regions, including hippocampus: GABAergic (Freund and Antal, 1988; Kiss et al., 1990), cholinergic (Mesulam et al., 1983), and glutamatergic (Colom et al., 2005; Manns et al., 2001; Manseau et al., 2005). Silencing of PV cells in medial septum during REM sleep led to decrease of theta oscillations and to impairment of spatial as well as fear-conditioned contextual memory (Boyce et al., 2016). Optogenetic activation of cholinergic MS cells affected hippocampal theta oscillations during quiet waking, but not during active waking in rats (Mamad et al., 2015). Likewise, optostimulation of cholinergic MS cells increased theta power in anesthetized mice but it decreased or had no effect on either theta power or locomotion in behaving mice (Vandecasteele et al., 2014). Stimulation of cholinergic fibers also increased firing of hippocampal inhibitory interneurons and made more precise coupling of pyramidal cell firing to theta phase (Dannenberg et al., 2015). Optogenetic activation of glutamatergic MS cells led to initiation of locomotion, preceded by theta oscillations, in head-fixed mice (Fuhrmann et al., 2015). In freely behaving mice, activation of glutamatergic neurons in the MS strongly synchronized hippocampal theta rhythms, whereas selective activation of MS glutamatergic projections to the hippocampus did not affect theta rhythms (Robinson et al., 2016), suggesting that MS glutamatergic neurons affect hippocampal theta oscillations through modulation of other septal neurons, e.g. parvalbumin (PV) cells, or hypothalamic generators of theta oscillations. Thus, behavioral effects of somatic MS optostimulation can partly be mediated by a direct activation of non-hippocampal targets in addition to

the entrainment of hippocampal theta oscillations. This complex interplay between MS, hippocampus and hypothalamic theta generators remains to be elucidated.

GABAergic cells in MS express PV (Freund, 1989) and play a key role in the generation and maintenance of hippocampal theta rhythm (Bender et al., 2015; Bland et al., 1999; Borhegyi et al., 2004; Hangya et al., 2009; Kocsis and Vertes, 1997; Wulff et al., 2009). PV cells in the MS provide extensive collateral innervation within the MS (Borhegyi et al., 2004), and their projections to hippocampus selectively target PV interneurons (Freund and Antal, 1988). Genetic ablation of inhibitory inputs to hippocampal PV interneurons (Wulff et al., 2009) or optogenetic silencing of these cells (Amilhon et al., 2015) disrupts theta oscillations. Theta-rhythmic inhibition of hippocampal PV interneurons by MS PV cells (Borhegyi et al., 2004) determines theta-rhythmic firing of pyramidal cells (Toth et al., 1997). In turn, pyramidal cells via MS-projecting interneurons (Blasco-Ibanez and Freund, 1995; Jinno et al., 2007; Manseau et al., 2008; Mattis et al., 2014; Toth et al., 1993) provide rhythmic feedback to MS, thus supporting maintenance of the theta rhythm (Hangya et al., 2009).

3.3 Subcortical circuits underlying the behavioral correlates of theta rhythm: nucleus incertus

As discussed in section 6 below, the hippocampus has long been associated with the potentially linked functions of arousal, stress-regulation and anxiety. How septo-hippocampal theta in particular might be linked to these functions remains unclear. Briefly, one approach has been to explore the ‘stress-reactive’ nucleus incertus in the pontine brainstem (reviewed in Ryan et al, 2011; Ma and Gundlach, 2015), which consists of largely GABAergic projection neurons, many of which express relaxin-3. The nucleus incertus has very dense projections not only to neurons in the medial septum and diagonal band which project to the hippocampal formation, but also to ventral regions of the hippocampal formation (i.e. temporal pole in rodents), notably to the ventral dentate gyrus and ventral subiculum (Goto et al, 2001; Ma and Gundlach, 2015). As discussed in section 6.1 below, it is the ventral, rather than the dorsal, hippocampus that has been associated with anxiety, especially unconditioned anxiety (Bannerman et al, 2004), thus exploring the nucleus incertus’ projections may be particularly relevant to understanding the hippocampal role in anxiety and stress. In the

anaesthetized rat, stimulation of the nucleus incertus elicits hippocampal theta, and disruption of the nucleus incertus attenuates theta elicited by stimulation of the reticularis pontis oralis (Nunez et al, 2006). A Granger causality analysis revealed causal interdependence between the neuronal activity in nucleus incertus and the hippocampus in the theta-state (Martinez-Bellver et al., 2017). Taken together, these findings suggest that the nucleus incertus has a rather significant role in controlling septo-hippocampal theta, including the reticular-elicited theta which has been used to assay anxiolytic drug efficacy (discussed in sections 6.1 and 6.2). One provocative mechanistic finding is that relaxin-3-positive neurons in the nucleus incertus are excited by ICV infusion of CRF and fire at a particular phase of hippocampal theta, while relaxin-3-negative neurons are unaltered/inhibited by CRF, and show no link to hippocampal theta (Ma et al, 2013). This direct link between stress signals and hippocampal theta may help to further explore emotional contributions to hippocampal theta in a way that integrates cellular variables, oscillations and function in the behaving animal. Relatedly, in section 6 below, we consider an approach to dissociating emotion-sensitive from cognitive components of theta frequency.

4.1 Hippocampal population activity during theta oscillations and rapid regulation of locomotion

While the correlation between hippocampal theta and locomotion has been known for a long time, it has remained elusive whether hippocampal theta follows locomotion (e.g. for spatial computations, see section 2 above), or can actually control locomotion. Vanderwolf (Vanderwolf, 1969) implicated changes in theta rhythmic activity in behavioral control of complex voluntary movements, whereas Grastyan and colleagues (Grastyan et al., 1965) suggested a role for theta oscillations in motivated behaviors. A study where theta oscillations in the hippocampus were induced (using electrical stimulation of MS) independent of behavior, showed a dissociation of hippocampal theta oscillations from its behavioral correlates (Kramis and Routtenberg, 1977), suggesting that theta oscillations do not directly induce locomotion. Lesions of hippocampus or septum are known to increase locomotor activity (Jarrard, 1968) and running speed (Kim and Frank, 2009), orienting reactions (reviewed in (Vinogradova, 1995) and the frequency of self-stimulation (Buno and Velluti, 1977), while electrical

stimulation of hippocampus led to the inhibition of voluntary movement (Bland and Vanderwolf, 1972b). Gaining control over regularity of theta oscillations using optogenetic theta-rhythmic stimulation of MS GABAergic projections in hippocampus, Bender et al., 2015 showed that hippocampal theta oscillations causally influence locomotion. Spontaneous theta oscillations episodes, comprising cycles of a more regular amplitude, occur during running at a slower and less variable speed (Fig. 1). Accordingly, optogenetic stimulation of MS GABA inputs, which rendered theta oscillations more regular, led to a more stable and slower running speed, while non-theta rhythmic stimulation of MS GABA inputs onto hippocampus did not affect locomotion (Bender et al., 2015). These findings suggest that hippocampus not only receives a movement-dependent bottom-up modulation from subcortical regions but also provides the top-down feedback to directly regulate locomotion.

LFP theta oscillations involve a manifold of neuronal activity dynamics (Buzsaki et al., 1983), ranging from rhythmic modulation of discharge probability to theta phase precession (O'Keefe and Recce, 1993) and cross-frequency coupling with gamma oscillations (Bragin et al., 1995; Buhl et al., 2003; Colgin et al., 2009; Wulff et al., 2009; Korotkova et al., 2010). This signaling involves pyramidal cells and various types of interneurons (Klausberger and Somogyi, 2008), i.e. the cells which participate in the generation of the theta rhythm, leading to a functional cross-talk between experience-dependent information processing and synchronization. Indeed, mutual relationships between properties of pyramidal cells' output and features of theta oscillations have been demonstrated. On the one hand, information about an animal's position can be extracted both from firing of pyramidal cells (section 2 above) and from spatiotemporal variations of theta oscillations amplitude (Agarwal et al., 2014); the firing of fast spiking interneurons, key generators of theta currents, is modulated by place cells according to animal's position (Maurer et al., 2006); and the routing of the spatial signal from MEC and CA3 to CA1 is tightly related to generation of theta-coupled gamma oscillations in distinct frequency bands (Colgin et al., 2009). On the other hand, theta-mediated rhythmic inhibition modifies firing probability during experience-dependent activation of a place cell, as firing probability computed for a particular theta phase is more consistent across theta cycles of more similar amplitudes (Bender et al., 2015). At a population level, the dynamics of the hippocampal output

involves at least three factors. The first determinant is the temporal consistency of the theta rhythmic inhibition related to fluctuations of population synchrony and LFP theta amplitude. The second dynamic factor is the nesting of slow and fast gamma oscillations to specific phases of the theta rhythm, (Colgin et al., 2009; Schomburg et al., 2014). The third factor is a population firing rate coding, which depends on global remapping of representations upon changes of spatial environment (Wills et al., 2005), on rate remapping due to variability of sensory input (Leutgeb et al., 2005; O'Keefe and Conway, 1978), reward representations (Dupret et al., 2010; McKenzie et al., 2014), or different types and sequences of memory episodes occurring in the same location (Ferbinteanu and Shapiro, 2003; Wood et al., 2000). Further, subcortical inputs adjust theta synchrony depending on ongoing behavior (Bland et al., 2006, Fuhrmann et al., 2015), and direct cholinergic and aminergic neuromodulatory inputs regulate hippocampal processing (Dannenberg et al., 2015; Takeuchi et al., 2016; Vandecasteele et al., 2014).

While it is clear that the processes described above shape temporal changes of the hippocampal population activity, specific readouts and functions of these changes remain elusive. Experiments performed in the 1960s to 1980s suggested that hippocampal efferents signal novelty (Meeter et al., 2004), assist orienting responses and planning of voluntary movements (Vanderwolf, 1969) and at the circuit level serve a function of behavioural inhibition (Gray 1982). These and other diverse behavioral phenomena could not be, however, clearly connected to selective cellular responses at any specific timescale, until the discovery of place cells (O'Keefe and Dostrovsky, 1971) and subsequent demonstration of a striking example of a temporal coding in the brain - hippocampal theta phase precession (O'Keefe and Recce, 1993). Recently, ensembles of hippocampal neurons have been demonstrated to directly trigger behaviors associated with their formation (Liu et al., 2012). Intricate dependence of place and grid cells' firing on experience, encoding of which involves firing sequences, organized with millisecond precision, makes experimental replay of their temporal activity particularly challenging. An essential temporal aspect of it, gamma oscillations (Colgin et al., 2009; Csicsvari et al., 2003; Schomburg et al., 2014), have been shown to support spatial working memory, when optogenetically facilitated in the CA1 to MEC pathway (Yamamoto et al., 2014).

Episodes of hippocampal theta oscillations, which have cycles of a similar amplitude, for hundreds of milliseconds or even seconds, are accompanied by a more constant hippocampal output and by running with a more regular and slower running speeds. Optogenetically increasing regularity of theta oscillations' amplitude led to the same effect on locomotion (Bender et al., 2015). This indicates a causal influence of the temporal variability of the hippocampal population output on the movement pattern regulation. Experience-dependent flexibility of hippocampal representations, different density of place fields depending on salient features of environment (Dupret et al., 2010; McKenzie et al., 2014) as well as variations in sensorimotor and cognitive processing (Ferbinteanu and Shapiro, 2003; Long et al., 2014; Leutgeb et al., 2005; O'Keefe and Conway, 1978; Wood et al., 2000) are the factors likely contributing to the variability of theta amplitude and of the hippocampal population output over time. These results suggest that dynamic collective aspects of hippocampal representations are essential for rapid control of behavior.

4.2 Subcortical read-out of theta rhythmic hippocampal signaling via lateral septum

The major subcortical output of the hippocampus is the lateral septum (LS), a GABAergic nucleus which receives non-reciprocal inputs from hippocampal pyramidal cells (Risold and Swanson, 1996) as well as from medial prefrontal cortex (Carus-Cadavieco et al., 2017) and is connected with several subcortical regions including lateral hypothalamus (Risold and Swanson, 1996), the ventral tegmental area (Luo et al., 2011) and amygdala (Sheehan et al., 2004). Chemogenetic inhibition of hippocampus to LS projections leads to an increase in running speed (Bender et al., 2015), pointing to a circuitry, the disruption of which underlies behavioral hyperactivity after lesions of hippocampus or LS (Sheehan et al., 2004). Further, theta oscillations are coordinated between hippocampus and lateral septum (Bender et al., 2015). This prominent coordination is specific for the theta band: coordination at gamma frequencies is much lower between hippocampus and LS than between medial prefrontal cortex and LS (Carus-Cadavieco et al., 2017). Optogenetic inhibition of the hippocampus to LS pathway precludes the regularizing effect of hippocampal theta oscillations on locomotion, suggesting that changes in hippocampal theta synchronization are translated

into rapid adjustment of running speed during spontaneous exploration via the LS. Further, theta oscillations are also suggested to be involved in regulation of motivated behavior. Ongoing hippocampal theta oscillations increased in amplitude and frequency before and after reward-associated lever pressing; the rats tended to lever press during particular phases of theta (Buno and Velluti, 1977); the phase of the theta wave at which lever pressing occurred was opposite to that at which lever releasing occurred (Semba and Komisaruk, 1978). Theta-frequency stimulation of hippocampus via LS-induced disinhibition activates dopaminergic VTA neurons, and this pathway supports reinstatement of reward memories (cocaine-seeking) by contextual stimuli, thus linking context with reward (Luo et al., 2011). LS neurons show place- and reward-related activity, suggesting possible coding of contextual information associated with reward (Takamura et al., 2006).

Another prominent efferent region of LS is the lateral hypothalamus (LH), which is crucial for control of locomotion (Gladfelter and Brobeck, 1962; Grastyan et al., 1965; Grillner et al., 2008; Sinnamon, 1993) and arousal (Herrera et al., 2016; Mileykovskiy et al., 2005). Many LH cells progressively increase their firing upon locomotion onset (Bender et al., 2015). Approach behaviors elicited by stimulation of LH, but not withdrawal behaviors, correlate with hippocampal theta oscillations (Grastyan et al., 1965). Theta-rhythmic activation of LS projections to the LH replicates the reduction of running speed, induced by more regular hippocampal theta oscillations (Bender et al., 2015) during spontaneous locomotion. LS afferents to the LH are also activated during cocaine preference (Sartor and Aston-Jones, 2012), suggesting involvement of this pathway in motivated behaviors.

5.1 Theta rhythm and coding of time for episodic memory.

In addition to its role in coding the “where” of memory, theta rhythm may also contribute to encoding the “when” of episodic memory. In addition to coding spatial location, neurons in the hippocampus and entorhinal cortex respond selectively at consistent time points within each trial of a behavioral task (Kraus et al., 2015; Kraus et al., 2013; MacDonald et al., 2013; MacDonald et al., 2011; Pastalkova et al., 2008). These responses have been referred to as “time cells” (MacDonald et al., 2011). The firing of time cells could allow events or items to be associated with a specific time

point coded by neural activity as well as a specific location coded by place cells. In an explicit timing task (DRL) hippocampal cells tend to code time features of the task that are not linked to narrow “time points” (Young and McNaughton N., 2000).

Neurons in the hippocampus and entorhinal cortex that code spatial location often code time intervals as well. This was initially shown in neurons of the hippocampus as a rat ran in a running wheel during the delay interval between different responses in a spatial alternation task (Pastalkova et al., 2008). Further studies explored these responses on a treadmill that allowed studies of systematic changes in the treadmill speed. On the treadmill, it was shown that neurons can code either the time of running or the distance of running, and many neurons that code these dimensions also fire as place cells in different locations in the task (Kraus et al., 2013). Modeling shows that the same framework used for modeling grid cells with theta rhythm oscillations (Burgess, 2008) could contribute to coding of time intervals by time cells (Hasselmo, 2008; Hasselmo, 2012; Hasselmo and Stern, 2014). This use of oscillations to code time intervals resembles previous models of time intervals (Brown et al., 2000; Miall, 1989). Consistent with predictions of this model, neurons in the entorhinal cortex that fire as grid cells during foraging in an open field will also fire as time cells during running on a treadmill (Kraus et al., 2015). Models of episodic memory show how the coding of time and space by theta rhythm oscillations could account for episodic retrieval (Hasselmo, 2009; Hasselmo, 2012) that could underlie the hippocampal activity found in functional magnetic resonance imaging (Brown et al., 2010; Brown and Stern, 2014).

5.2 Theta rhythm separation of encoding and retrieval.

The behavioral data above indicates a role of theta rhythm in memory function, but the mechanisms for this role are not known. One possible model shows how specific physiological processes at different phases of theta rhythm oscillations could enhance encoding by separating the dynamics of encoding and retrieval on different phases of the theta rhythm (Hasselmo et al., 2002). In this model, during the encoding phase of each theta cycle, input from entorhinal cortex is strong, as shown by current source density analysis (Brankack et al., 1993; Buzsaki et al., 1986). Synaptic input from region CA3 is weaker at this phase, but synaptic modification at the CA3 synapses is

strong, storing associations between the presynaptic activity in CA3 and the postsynaptic activity from entorhinal cortex. Physiological data shows that long-term potentiation is strongest at this phase of the EEG (Hölscher et al., 1997; Huerta and Lisman, 1995; Hyman et al., 2003).

During a separate retrieval phase of each theta cycle, input from entorhinal cortex is weaker, but the excitatory input from region CA3 is stronger (Brankack et al., 1993; Buzsaki et al., 1986). The strong input from CA3 means postsynaptic activity is driven by previously modified synapses, retrieving previously stored associations. At this time, the cell body receives the least inhibition, allowing retrieval to drive the spiking output of the neurons. Long-term potentiation is reduced during this time, so that the retrieval activity is not stored as a new event. Simulations show that separate phases of encoding and retrieval allow effective separation of new external input from prior retrieval (Hasselmo et al., 2002).

Physiological data on theta rhythm are consistent with the encoding/retrieval model. At one phase of theta, the dendrites are depolarized (Kamondi et al., 1998), allowing encoding of entorhinal input, while the cell body is hyperpolarized, preventing spiking due to interference from retrieval of previous associations, (Hasselmo et al., 2002). Membrane potential changes could arise due to different morphological classes of inhibitory interneurons that spike at different phases of theta rhythm (Klausberger et al., 2003; Klausberger and Somogyi, 2008). Inhibitory axo-axonic and basket cells could inhibit the cell bodies and axons of excitatory cells to reduce spiking output during encoding (Cutsuridis and Hasselmo, 2010). At the opposite phase, oriens lacunosum-moleculare cell spiking inhibits the layer where entorhinal input contacts the distal dendrites, reducing external input during retrieval of associations at previously modified synapses in stratum radiatum (Hasselmo et al., 2002; Kunec et al., 2005).

The model helps the understanding of impairments of memory encoding during loss of theta rhythm (Chrobak et al., 1989; Givens and Olton, 1994; M'Harzi et al., 1987; Winson, 1978). The model is consistent with physiological data showing that the phase of theta rhythm resets during stimulus encoding (Givens, 1996), and in rats performing a delayed non-match to sample task, spiking occurs at different phases of theta for match (retrieval) versus non-match (encoding) stimuli (Manns et al., 2007). One study tested predictions made by combining the cholinergic model (Hasselmo et al., 1996) and theta

phase model (Hasselmo et al, 2002) of encoding vs retrieval separation (Douchamps et al, 2013). In the cholinergic model, high levels of acetylcholine promote the encoding mode. As predicted, replicating an earlier study (Lever et al, 2010), environmental novelty shifted CA1 place cell firing to a later phase of theta (towards the pyramidal-layer theta peak), consistent with a bias towards novelty-elicited coding; scopolamine (a cholinergic antagonist) shifted cell firing in a familiar environment to an earlier phase of theta (towards the pyramidal-layer theta trough), consistent with an anti-encoding bias favouring retrieval. Moreover, in a novel environment, scopolamine blocked the later-phase-in-novelty effect, and blunted place cell remapping, consistent with both models (Hasselmo et al, 1996; Hasselmo et al, 2002). The behavioural relevance of these kinds of observations was tested by an optogenetic study that used closed-loop stimulation to show a pattern of memory enhancement consistent with the idea that stimulation at one phase of theta promoted encoding while stimulation at another phase promoted retrieval (Siegle and Wilson, 2014). Consistent with the encoding phase of the model, high frequency gamma oscillations are coherent between entorhinal cortex and region CA1 at one phase of theta (Colgin et al., 2009), and coherent between CA3 and CA1 at a different phase (Belluscio et al, 2012; Colgin et al, 2009; Schomburg et al, 2014).

6.1 Dual functionality of the hippocampal formation?: links to theta rhythm

There is no theoretical consensus as to how best to uniquely characterise hippocampal function. Broadly speaking, two sets of functional associations persist, one cognitive, the other emotional. In the first set, the hippocampus supports spatial cognition, episodic and other memory, with these functions typically linked to coding for, and detecting initially novel contexts (to which individual contents can be associated), (e.g. Burgess et al., 2002; Hasselmo et al., 1996; O'Keefe and Nadel, 1978; Schiller et al., 2015). Briefly, paradigmatic findings in this set include the discovery of hippocampal spatial cells (reviewed in: Hartley et al., 2014), online and offline (re)activation of experience-specific cell firing sequences (reviewed in O'Neill et al., 2010; Redish, 2016; Schiller et al., 2015) and evidence for hippocampal support of context-dependent memory (e.g. O'Keefe and Nadel, 1978; Phillips and LeDoux, 1992; Redondo et al., 2014). In the second set, rather differently, the hippocampus plays a crucial role in anxiety, likely linked to roles in stress and depression. Paradigmatic

findings in this set include demonstrations of anxiety-modulating effects following hippocampal disruption (reviewed in Engin and Treit, 2007; Gray and McNaughton N., 2000), the importance of hippocampal neurogenesis in controlling anxiety (e.g. Revest et al., 2009) and depression (e.g. Santarelli et al., 2003), and hippocampal control over the HPA axis (Herman and Cullinan, 1997; Sapolsky and Meaney, 1986).

Remarkably few theoretical studies try to bridge the gap between these two sets of functional associations. While the anxiety-based approach accounts for the considerable context-conditioned fear literature in terms of ‘anticipatory anxiety’ (Gray and McNaughton N., 2000), its attempt to incorporate the growing spatial literature has not been influential. While a context-based memory approach naturally explains context-conditioned fear literature, it fails to account for hippocampal contributions to unlearned anxiety. The problem of bridging these literatures seems more acute when we consider that proponents of different theories of hippocampal function place theta at the heart of their theory. For instance, O’Keefe and Nadel (1978) reinterpreted observations from Vanderwolf (1969) linking theta to voluntary movement to suggest that theta acted as an index of spatial translation, and it is now clear that there are robust links between theta phase and spatial variables in linear tracks and open fields (Climer et al., 2013; Huxter et al., 2008; Jeewajee et al., 2014; O’Keefe and Recce, 1993; Skaggs et al., 1996). Similarly Gray (1982) argued that hippocampal theta was crucial for behavioural inhibition, emphasising how all drugs which were clinically effective anxiolytic drugs impaired rodent septo-hippocampal theta.

By far the most influential approach to duality of hippocampal function has been to posit that the dorsal and ventral hippocampus are distinct structures, with space/memory assigned to dorsal hippocampus (posterior in primates), and anxiety to ventral hippocampus (anterior in primates) (Bannerman et al., 2004; Fanselow and Dong, 2010; Strange et al., 2014). This view receives clear support from lesion studies in animals (Bannerman et al., 2004; Kjelstrup et al., 2002; Pentkowski et al., 2006), and neuroimaging studies in primates including humans (Bach et al., 2014; Loh et al., 2016; O’Neil et al., 2015; Oler et al., 2010). This anatomy-based approach clearly captures an important truth about the parcellation of hippocampal function. However, an extreme version of this approach is incompatible with hippocampal physiology, not least because hippocampal theta is found throughout the dorso-ventral axis and resembles a single

travelling wave (Lubenov and Siapas, 2009; Patel et al., 2012). In other words, while amplitude can vary, and phase does vary systematically, along the dorso-ventral axis (Hinman et al., 2011; Patel et al., 2012), as far as frequency is concerned the dorsal and ventral hippocampus both share the same theta in the intact behaving rat. Indeed, the vast majority of studies inspiring and supporting the Gray and N. McNaughton theory of anxiety (Gray, 1982; Gray and McNaughton N., 2000), including where anxiolytic drugs reduce the frequency of reticular-elicited theta, have sampled *dorsal* hippocampal theta (e.g. dorsal sampling: Engin et al., 2008; Gray and McNaughton N., 2000; McNaughton N. et al., 2007; Seidenbecher et al., 2003; Shin et al., 2009; Siok et al., 2009; Yeung et al., 2012) (dorsal & ventral sampling: Adhikari et al., 2010; Cornwell et al., 2008; Engin et al., 2016).

6.2 Dual functionality of the hippocampal formation: two components of theta frequency

In summary, it remains unclear how the hippocampal processing subserving such different functions, space/memory on the one hand, and anxiety on the other, might be mechanistically related to each other, when both share an important physiological substrate: septo-hippocampal theta. One reasonable theoretical starting assumption is that the processing of one set of functions should not interfere with the processing of the other. If theta frequency is linked to both spatial translation and anxiety, it would be maladaptive for anxiety to be reduced if running speed were to be reduced, or path integration mechanisms impaired. One would expect to show some independence of theta mechanisms relating to spatial cognition and anxiety. Here, we highlight one such approach, begun by Wells et al. (2013).

The oscillatory-interference model of grid cell mechanisms (discussed above in section 2.2) suggested that theta frequency overall might result from the additive contribution of two components, one corresponding to the slope of the theta frequency to running speed relationship, and one corresponding to the variable offset of this relationship, defined by its intercept on the speed (Y) axis at 0cm/s (Burgess, 2008). Importantly, in this model, the two contributions to frequency are independent. The scale of spatial coding is determined by the rate of change of frequency with running speed, while the absolute value of the baseline frequency itself (the intercept) is

irrelevant to spatial coding.

The idea that spatial scale increases in environmental novelty (Barry et al., 2012b) is a strong prediction of the oscillatory interference models (Burgess, 2008; Burgess et al., 2007), given that theta frequency is reduced in environmental novelty (Jeewajee et al., 2008b). More specifically, the Burgess (2008) model predicts that the increase in spatial scale in novelty results from a decrease in the slope of the theta frequency to running speed relationship. Thus the Wells et al. (2013) study made specific predictions regarding the spatial cognition functional association of hippocampal theta: a novel spatial context would reduce the *slope* of the theta frequency to running speed relationship, without any obligatory effect on intercept, and this would increase spatial scale, with the level of slope change predicting the level of scale change (place field size).

Combining the Burgess (2008) model with insights from the Gray and McNaughton N. (2000) theoretical approach, the Wells et al. (2013) study derived a new prediction regarding the ‘anxiety’ functional association of hippocampal theta. Intriguingly, all clinically-effective anxiolytic drugs (i.e. prescribed for Generalised Anxiety Disorder) reduce the average frequency of hippocampal theta elicited by stimulation of the reticular formation (‘reticular-elicited theta’). This frequency-reduction effect of reticular-elicited theta is seen across a wide range of *anxiolytic* drugs, despite their substantial neurochemical dissimilarities (McNaughton et al 1986; McNaughton and Coop, 1991; Engin et al., 2008; McNaughton N. et al., 2007; Siok et al., 2009; Yeung et al., 2012), but is not seen with *antipsychotic* drugs (Gray and McNaughton N., 2000). In addition, ‘immobility-related’ type II theta occurs during predator-elicited arousal/anxiety (Sainsbury et al., 1987), and during ‘anticipatory anxiety’ (Gray and McNaughton N., 2000) following standard-footshock conditioning (Seidenbecher et al., 2003). Accordingly, since: a) anxiety may be linked to type-II theta; b) anxiolytics reduce reticular-elicited theta frequency; and c) the Burgess (2008) model links type II theta mechanisms to intercept, the prediction was that anxiolytics should reduce the *intercept* of the theta frequency to running speed relationship, without any obligatory effect on slope. In summary, a double dissociation was predicted whereby anxiolytics would specifically reduce y-intercept, and environmental novelty would specifically reduce slope.

6.3 Different types of anxiolytic drug reduce the y-intercept of the theta-frequency-to-running speed relationship.

This prediction was fulfilled in the experimental results (Wells et al., 2013). Figure 2 shows schematic illustrations of the data. Figure 2F shows the effect of systemic injection of two well-established clinically effective anxiolytic drugs (Chlordiazepoxide, a benzodiazepine agonist; Buspirone, a 5HT-1A agonist) and one putative anxiolytic drug (O-2545, a CB1 agonist) which reduced thigmotaxis, as expected from a classic anxiolytic drug. At the doses tested, all the anxiolytic drugs elicited a reduction in the y-intercept without affecting slope. Further support for the generality of these findings comes from unpublished work (presented in Lever et al., 2016) showing that systemic injection of pregabalin also reduces the y-intercept (Figure 2F). Pregabalin is a presynaptically-acting anti-epileptic drug which binds to the α_2 - δ -1 subunit of voltage-gated calcium-channels on presynaptic sites, effectively blocking these channels. Significantly, it is now clear that Pregabalin is also an effective anxiolytic drug (in the European Union, where it is licensed for anxiolysis).

It is interesting that the specific effect of y-intercept reduction in hippocampal theta from the freely moving rat is shared by all these anxiolytic drugs tested, despite the considerable variance in primary targets (benzodiazepine site of GABA-A receptor, 5HT-1A receptor, CB1 receptor, α_2 - δ -1 subunit of calcium-channel) and the presynaptic and postsynaptic locations of these targets (e.g. presynaptic α_2 - δ -1 subunit containing calcium-channel, postsynaptic benzodiazepine site of GABA-A receptor). Furthermore, this specific y-intercept reduction effect during freely moving theta is consistent across different drug classes, unlike that obtained from the reticular-stimulation model, where anxiolytic drugs reduce the slope and/or intercept of the frequency-to-intensity function (Gray and McNaughton N., 2000; McNaughton N. et al., 2007). For instance, at the doses tested, Chlordiazepoxide reduced only the slope, while Buspirone reduced only the intercept, of this function (summarised in (John et al., 2014)) in the reticular-stimulated theta.

How widely across septo-hippocampal theta sites does this specific effect on frequency extend? Interestingly, the observations from hippocampal theta have been replicated and extended by demonstrations that systemic injections of a benzodiazepine

(Diazepam) and a 5HT-1A agonist anxiolytic (8-OH-DPAT) all reduce the y-intercept of theta recorded from the entorhinal cortex of freely moving rats (Fig 2G depicting schematic illustrations; Monaghan et al., 2015; Monaghan et al., 2014).

Taken together, this shared and specific effect of different classes of systemically-administered anxiolytic drugs on septo-hippocampal theta in behaving rats strongly hints at an underlying common mechanism of anxiolysis, an understanding of which is absent from reviews of anxiolytic drugs (e.g. Sandford et al., 2000). Even if the y-intercept reduction is a proxy to a more fundamental mechanism of systemic anxiolysis, these findings should help to stimulate rational approaches to drug design, e.g. (John et al., 2014; McNaughton N. et al., 2007).

6.4 The slope of the theta-frequency-to-running speed relationship: modulation by environmental novelty

Figure 2 shows a schematic figure of the effect of introducing the rat into a novel spatial context, i.e. a novel configuration of cues (which elicited remapping) in the same geocentric location as a familiar baseline environment. In line with a central prediction of the oscillatory interference model (Burgess, 2008), the contextual novelty elicited a reduction in the slope without significantly affecting intercept (Wells et al., 2013) (Figure 2D). Moreover, as predicted by the Burgess (2008) model, place fields of CA1 place cells expanded in the novel environments (Figure Figure 2D), and a robust correlation was observed between the change in slope across the baseline and novel environments, and the change in the spatial scale (i.e. average field size) of the place cells. Partial correlation analysis showed that slope change predicted spatial scale change controlling for the effect of novelty status, but not vice versa. These results were consistent with the (Barry et al, 2012b) study, where environmental novelty elicited an expansion in the spatial scale of entorhinal grid cells (Figure 2E). In the oscillatory interference model (Burgess, 2008), this is due to flattening of slope, which the (Barry et al, 2012) study did not examine. Specifically, what controls spatial scale in the model is the gain of the intrinsic (i.e. interburst) theta frequency of cell firing due to speed, which is harder to analyse than the LFP (but see Hinman et al, 2016).

Furthermore, the hippocampal theta study (Wells et al, 2013) also found that, rearing on the hind legs, a hippocampus-dependent behaviour highly sensitive to

environmental novelty (Lever et al., 2006), increased when slope was flatter (Figure 2D), and that rearing frequency was robustly predicted by changes in slope, but not intercept. This further supported the theoretical link between slope and environmental novelty.

The Wells et al. (2013) study also observed a dissociation between slope and intercept that was not theoretically predicted. Only a few studies have investigated the positive relationship between temperature and theta frequency (e.g. Whishaw and Vanderwolf, 1971). The Wells et al. (2013) study showed that, in the locomoting rat at least, temperature is positively correlated with the slope, but not the intercept, of the frequency-speed relationship. The dissociation may also prove useful in understanding mechanisms driving underlying type I theta frequency modulation.

6.5 Dual functionality and theta frequency: overview

Taken together, this set of findings dissociating intercept reduction and slope reduction provide good support for the additive two component model of hippocampal theta in Burgess (2008), and offer a new physiological perspective upon dual hippocampal functionality. Whether oscillatory interference is a crucial mechanism for grid cell generation remains controversial (Barry et al., 2012a; Brandon et al., 2011; Koenig et al., 2011; Yartsev et al., 2011), but it seems intuitive that the slope component of theta frequency is linked to distance estimation (see also McNaughton B.L. et al., 2006). Recent hints of this are the demonstrations that: 1) darkness in mice flattens the slope component of theta frequency, and also disrupts grid fields (Chen et al., 2016) (Figure 2E); 2) medial septum inactivation flattens the slope of the intrinsic spiking rhythmicity of individual neurons (Hinman et al, 2016) and also disrupts grid fields (Brandon et al, 2011). Whether space is physical or semantic (Constantinescu et al., 2016), whether physically traversed or imagined (Horner et al., 2016), a crucial process for mapping is estimating the distance (and direction) from one place to another, and theta may contribute to this process. Accordingly, the demonstration that the y-intercept and slope components can be modulated independently in the freely behaving rat is potentially significant. In summary, the preliminary and published work described here (e.g. Lever et al., 2016; Monaghan et al., 2015; Monaghan et al., 2014; Wells et al., 2013) may help to lay the empirical groundwork for a quantitative approach to

hippocampal theta that bridges parallel streams of research on hippocampal cognitive and emotional processing.

7.1 The post-natal development of theta and the cognitive map

Rats and mice, like humans, are altricial animals, born possessing only very limited sensory and motor capabilities (Alberts, 1984). By the age of three weeks, however, rats are capable of independent feeding, movement, and display hippocampus-dependent spatial learning and memory (for a review see (Wills et al., 2014)). In the following sections, we will discuss the post-natal emergence of the hippocampal theta rhythm in the rat, relating this to the development of wider hippocampal neural networks underlying spatial cognition, as well as the emergence of spatial behaviour. We aim to show that the development of the theta oscillation during this three-week window can provide insights how it supports hippocampal function.

7.2 Early emergence of network oscillations in the hippocampal formation

For approximately the first week of life, rats are not capable of sustained independent locomotion, and instead spend their time amongst a small group (or ‘huddle’) of littermates (Alberts and Brunjes, 1978). During this period, theta is not present in the hippocampal local field potential (LFP). Instead, the earliest co-ordinated network activity *in vivo* takes the form of large, slow deflections which reverse polarity across the CA1 pyramidal cell layer, which are seen from post-natal day 2 (P2) onwards (Leinekugel et al., 2002; Mohs et al., 2007). These are consistent with the Large Irregular Activity (LIA) state of the adult hippocampus, seen during rest and immobility in adults (Vanderwolf, 1969), and may also correspond to the giant depolarising potentials (Ben-Ari et al., 1989) seen in immature hippocampal slices *in vitro* (Leinekugel et al., 2002). The early emergence of such large, synchronous activity bursts has led to the proposal that they are required to develop basic network connectivity in the hippocampal formation (Ben-Ari, 2001; Buzsáki, 2015). Interestingly, the 140-200Hz fast oscillations (or ‘ripples’), which accompany LIA spikes in the CA1 layer (Buzsáki et al., 1992; O’Keefe and Nadel, 1978), emerge later, from one week of age onwards (Buhl et al., 2005; Mohs et al., 2007).

Rats are capable of crawling from approximately P9 (though *spontaneous* movement away from the nest occurs much later, at around two weeks) (Altman and Sudarshan, 1975; Gerrish and Alberts, 1996; T. J. Wills et al., 2014). At approximately this age, hippocampal theta is seen in vivo in awake animals for the first time (Mohns and Blumberg, 2008). (Though theta can be observed earlier in animals under urethane anaesthesia (Brockmann et al., 2011; Hartung et al., 2016)). Immature rats spend a large proportion of their time in a behavioural state known as ‘active sleep’ characterised by twitches of the limbs, head and eyes (Gramsbergen et al., 1970), and the earliest bouts of hippocampal theta co-occur with such myoclonic twitches during active sleep. These earliest instances of theta are also associated with bouts of gamma oscillations and bursts of hippocampal neural firing (Mohns et al., 2007; Mohns and Blumberg, 2008), raising the possibility that theta, early in development, may facilitate the fine-scale synchronisation of neural firing across hippocampal networks (Mohns and Blumberg, 2010).

Theta in adult rats (and other rodents) has been described as consisting of two different components, dissociable by their pharmacology and behavioural correlates: type I theta is related to movement, and is insensitive to blockade of the cholinergic projections to the hippocampus, type II theta occurs during alert immobility and is disrupted by application of cholinergic antagonists (Kramis et al., 1975). At P10, both types of theta appear to be present: atropine-sensitive theta emerges concurrently with theta associated with voluntary movement (Leblanc and Bland, 1979). This is consistent with the development of the cholinergic neurons in the medial septum, which develop gradually between P1 and P16, but display molecular markers of acetylcholine production by P10 (Bender et al., 1996). However, it has also been suggested that the early association of theta with myoclonic twitches (at P8) indicates that type I theta is the earliest to emerge (Mohns and Blumberg, 2008). As type I theta is thought to be supported by GABA-ergic projections from the medial septum to hippocampal interneurons (Buzsaki, 2002), early development of type I theta would be consistent with the very early development of GABA-ergic neurons in the medial septum (Bender et al., 1996), and the early development of inhibitory synapses onto CA1 pyramidal cells (Danglot et al., 2006). The finding that early hippocampal theta bursts can entrain the firing of neurons in other brain regions, for example the pre-frontal and para-

hippocampal cortices, indicates that the role of theta in synchronising developing networks may also extend beyond the hippocampal formation (Brockmann et al., 2011; Hartung et al., 2016).

The earliest bouts of theta display a markedly lower frequency than that observed in adults, displaying a frequency of around 5Hz (Leblanc and Bland, 1979; Mohs and Blumberg, 2008). Similar theta frequency increases are observed in other species (Marley and Key, 1963; Creery and Bland, 1980), suggesting that this might be a general pattern of mammalian brain development. *In vivo* recordings of hippocampal neural activity during exploration between P16 and P30 (Langston et al., 2010; Wills et al., 2010) show that the frequency of theta continues to increase gradually throughout this period, but remains lower than that of adult rats even after three weeks of age (Wills et al., 2010). As discussed in previous sections, the instantaneous frequency of theta is modulated by running speed in adult rats, and the intercept and the slope of the speed-frequency curve may reflect different aspects of hippocampal function (see sections 6.2, 6.3 and 6.4). During development, the frequency of theta is also positively modulated by running speed, from the earliest ages at which exploration occurs (Wills et al., 2010). Both the slope and the intercept of the speed-frequency curve increase during development, though the time course of their respective increases appears dissociable, with large changes in intercept occurring between P18 and P24, despite much slower, gradual changes in slope (Wills et al., 2010). Interestingly, other speed-related signals in the hippocampal formation, such as the speed-modulation of grid cells in the entorhinal cortex (Hinman et al., 2016), are also present early in development (Wills et al., 2012).

7.3 Modulation of neural firing by theta during development

The hippocampus contains several different classes of neurons whose firing is modulated by the position and orientation of the animal in space. A series of recent studies have shown that different types of spatially modulated neurons follow different developmental trajectories: head direction cells emerge first, abruptly, becoming adult-like as soon as animals open their eyes (Tan et al., 2015). Place cells are present as soon as animals begin to explore their environment (around P15, but with considerably reduced spatial tuning than in adulthood, and continue to mature gradually over the following 2-4 weeks (Scott et al., 2010; Wills et al., 2010). Finally, grid cells emerge

abruptly at around three weeks of age (Wills et al., 2010). For a review, see (Tan et al., 2016). In the adult, the probability of spiking of both place cells and grid cells is modulated by the phase of the ongoing theta oscillation (Fox et al., 1986; Hafting et al., 2008): in this section we will discuss how this temporal modulation of spiking by theta emerges during development.

Place cell spiking occurs preferentially on the negative phase of the locally recorded (CA1) theta oscillation (Fox et al., 1986), and the resulting theta frequency bursting is most clearly measured as a set of repeating peaks, at theta frequency, in the temporal auto-correlogram of the spike train. This theta-modulation of place cell spiking is present at the earliest ages tested (P16), but at lower levels than observed in adults (Langston et al., 2010; Wills et al., 2010). Interestingly, the degree of theta-modulation of place cells appears to reach adult-like levels at P22 (Wills et al., 2010), approximately coincident with the emergence of hippocampal spatial behaviours. An open question is whether the preferred phase of place cell firing also changes during development: different phases of the theta cycle have been proposed to coordinate the CA1 place cell firing with firing in different input areas, for example CA3 or entorhinal cortex (Hasselmo et al., 2002): changes in the preferred phase during development could reflect changes in the relative weights of input from these different regions.

The modulation frequency of adult place cell spiking (or ‘intrinsic frequency’) has a marginally greater frequency than the ongoing LFP theta, with the result that the phase of LFP theta at which spiking occurs precesses slightly as rats move through a place field (O’Keefe and Recce, 1993). Spike phase correlates better with distance travelled through the place field than with other variables (Huxter et al., 2003), leading to the idea that phase precession may represent a temporal code for space. Phase precession is a feature of grid cell, as well as place cell, firing, and these observations inspired ‘oscillatory interference’ models of spatial firing (Blair et al., 2008; Burgess et al., 2007; Zilli and Hasselmo, 2010). The common mechanism shared by such models is that a frequency difference between two oscillations, (where one of oscillation is frequency-modulated by velocity), can track the distance an animal has travelled and thereby produce spatially stable firing.

During development, the intrinsic frequency of both grid and place cells is higher than that of LFP theta, from the earliest ages at which spatial responses are

present (P16) (Langston et al., 2010; Wills et al., 2010). Phase precession through a place field is present at least as early as P17 in place cells (Langston et al., 2010; Wills et al., 2010), demonstrating that this temporal organisation of place cell spiking is potentially adult-like during earliest exploration. One avenue for further investigation is to use recently developed analysis methods (Climer et al., 2015) to test whether, during development, intrinsic frequency is modulated by running speed as it is in adult rats (Jewajee et al., 2008; Stensola et al., 2012; Hinman et al., 2016).

Outlook

The findings reviewed here show that hippocampal theta oscillations are crucial for diverse brain functions, ranging from anxiety and locomotion to cognitive processes. They also highlight the mechanisms through which hippocampal theta oscillations are involved in such a wide range of behaviors. First, the precision of hippocampal signalling and the temporal regularity of hippocampal output is related to several components of theta oscillations - frequency, amplitude and different phases of theta cycles. While frequency of hippocampal theta likely depends on bottom-up movement-dependent signals from cortical and subcortical theta generators, regularity of theta amplitude adjusts top-down output to subcortical targets, which then directly regulates locomotion. Influence of hippocampal theta rhythmic output regularity on locomotion may further reflect differential involvement of hippocampus in circuitries controlling spatial navigation depending on the familiarity of environment and other salient stimuli. Dissociation of theta signaling components, such as intercept reduction and slope reduction offers a new physiological perspective upon dual hippocampal functionality, helping to bridge the rather different views of hippocampal function in cognitive processes and anxiety. This quantitative approach to hippocampal theta may help to lay the empirical groundwork that bridges parallel streams of research on hippocampal cognitive and emotional processing. The complex interplay between multiple theta generators can also ensure precision of hippocampal signaling, crucial for separation of encoding and retrieval as well for theta phase precession. Impairments of this precision may underlie impairments of memory encoding upon loss of theta rhythm. Second,

different functions of theta oscillations can be mediated through signalling to various projections of hippocampus. Projection-specific inhibition or excitation of these pathways will enable investigation of particular pathways' contributions in different behaviors. Closed-loop, optogenetically induced, modifications or disruptions of theta oscillations during specific phases of behavioral tasks can probe for the necessity of theta oscillations for particular functions.

Maturation of theta oscillations in parallel with development of more complex behaviors in early postnatal days and weeks also points out the importance of theta-rhythm. During development, the intrinsic frequency of both grid and place cells is higher than that of LFP theta, from the earliest ages at which spatial responses are present (P16). Phase precession through a place field is present at least as early as P17 in place cells, demonstrating that this temporal organisation of place cell spiking is potentially adult-like during earliest exploration. One avenue for further investigation is to use recently developed analysis methods to test at what age intrinsic frequency is modulated by running speed in developing pups, as it is in adults, and as oscillatory interference models would predict.

These and future findings help to understand how oscillations participate in generation and regulation of complex behaviors, what role they play in healthy brain and how impairments of oscillations are linked to brain disorders.

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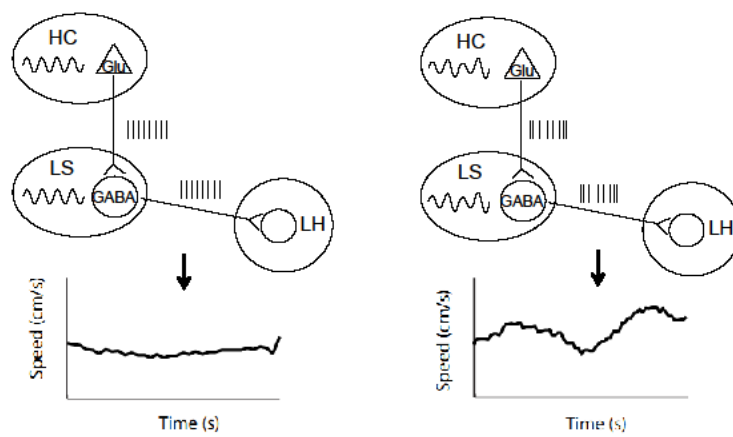
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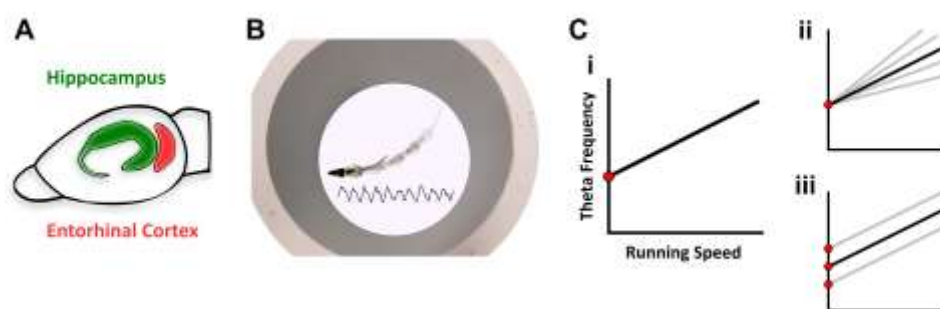
Figure legends

Figure 1 A schematic illustration of locomotion speed-regulating downstream theta-rhythmic signaling, which regulates locomotion speed (Bender et al., 2015). HC-hippocampus, LS-lateral septum, LH-lateral hypothalamus. The figure is a courtesy of Franziska Bender.

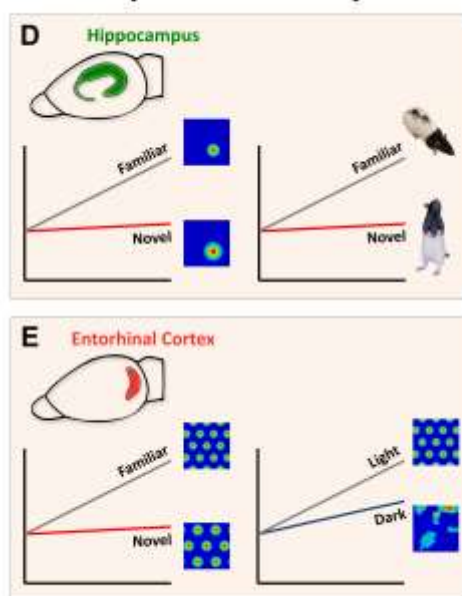
Figure 2 Functional dissociation of two components of hippocampal formation theta frequency (schematic illustrations)

Extracellular electrophysiological recordings in the hippocampal formation (**A**) show theta-band oscillations as the rat forages (**B**). One second trace of the local field potential showing ~10 cycles of theta (filtered 0.25 to 200Hz) is shown below rat (**B**). Whole-trial LFP data can be used to construct plot of instantaneous theta frequency vs running speed, showing correlation that is positive and broadly linear (**Ci**). Right-hand plots show potential modulation of slope (**Cii**) and y-intercept (**Cii**) values. Note Y-Intercept value (i.e. theta frequency at zero running speed), depicted as small red circle in each plot, is calculated from extrapolating frequency-speed regression line, not stationary behaviour. **D-G** show schematic illustrations of modulation of slope component (**D-E**), and y-intercept component (**F-G**). Environmental novelty (new spatial context) elicits reduction of slope in hippocampal and entorhinal theta. Slope reduction in hippocampus is accompanied by larger spatial scale of CA1 place fields (**D, left**) and increase in rearing on hindlegs, a hippocampal dependent novelty-responsive behaviour (**D, right**) (Wells et al, 2013). Environmental novelty elicits larger spatial scale of grid cells (**E, left**: Barry et al, 2012b), which (Burgess, 2008) model predicts is due to slope reduction (prediction, not data). Darkness elicits slope reduction in mice, accompanied by strong disruption to grid cell spatial signal (**E, right**: Chen et al, 2016). Different classes of systemically-administered anxiolytic drugs have the common effect of reducing y-intercept in theta from the hippocampus (**F**) and entorhinal cortex (**G**). Hippocampal theta: Chlordiazepoxide, Buspirone and O-2545 from (Wells et al, 2013); Pregabalin from (Lever et al, 2016); Entorhinal theta: Diazepam and 8-OH-DPAT (schematic illustration based on unpublished work in (Monaghan et al, 2014; Monaghan et al, 2015)).





Space & Novelty



Anxiolytic Drugs

